ClinicalEvidence

Diabetes: glycaemic control in type 1

Search date February 2010

Lalantha Leelarathna, Rustom Guzder, Koteshwara Muralidhara, and Mark L Evans

ABSTRACT

INTRODUCTION: Type 1 diabetes occurs when destruction of the pancreatic islet beta cells, usually attributable to an autoimmune process, causes the pancreas to produce too little insulin or none at all. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of intensive treatment programmes, psychological interventions, and educational interventions in adults and adolescents with type 1 diabetes? What are the effects of different insulin regimens or frequency of blood glucose monitoring in adults and adolescents with type 1 diabetes? We searched: Medline, Embase, The Cochrane Library, and other important databases up to February 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 42 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: different frequencies of insulin administration (continuous subcutaneous insulin infusion compared with multiple daily subcutaneous insulin injections), different frequencies of blood glucose self-monitoring (including continuous blood glucose monitoring compared with intermittent/conventional monitoring), educational interventions, intensive treatment programmes, and psychological interventions.

QUESTIONS

INTERVENTIONS

INTENSIVE TREATMENT PROGRAMMES, PSYCHOLOGICAL INTERVENTIONS, AND EDUCATIONAL INTERVENTIONS

Likely to be beneficial

Unknown effectiveness

INSULIN REGIMENS AND BLOOD GLUCOSE MONITORING

Likely to be beneficial

Covered elsewhere in Clinical Evidence

Diabetes: prevention of cardiovascular events

To be covered in future updates

Different types of insulin compared with each other

Closed-loop insulin delivery systems

Key points

- Type 1 diabetes occurs when destruction of the pancreatic islet beta cells, usually attributable to an autoimmune process, causes the pancreas to produce too little insulin or none at all.

  The prevalence of type 1 diabetes is 0.02% in people aged 0 to 14 years, and it is estimated that 479,000 people in this age group have type 1 diabetes worldwide.

  Although type 1 diabetes usually accounts for only a minority of the total burden of diabetes in a population, it is the predominant form of the disease in younger age groups in most resource-rich countries.
- Glycaemic control typically worsens in adolescence, owing to a combination of physical and psychological change and development.
- There is some evidence that educational and psychosocial interventions may improve glycaemic control and quality of life in adults and adolescents with type 1 diabetes.
- Intensive treatment programmes in adults and adolescents seem to improve glycaemic control compared with conventional treatment, and also seem to improve long-term outcomes (such as retinopathy, neuropathy, and macrovascular events), but they require a considerable investment of time and resources.

Better glycaemic control is also associated with higher rates of hypoglycaemia, the risk of which may be reduced with the judicious use of modern technology such as continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring.

- While regular self-monitoring of blood glucose is recommended to adults with type 1 diabetes, outside the setting of intensive and structured insulin-management programmes, such as DAFNE (Dose Adjustment for Normal Eating training), there are no reliable data on which to base advice about optimum frequency of blood glucose self-testing.
- However, the use of continuous glucose monitoring (allowing real-time insulin dose adjustments) may improve glycaemic control in adults compared with intermittent/conventional monitoring.
- We don't know whether psychological interventions improve glycaemic control compared with control. They may improve some psychological outcomes; however, evidence was weak and inconsistent.
- Continuous subcutaneous insulin infusion seems effective at improving glycated haemoglobin levels and quality of life compared with multiple daily subcutaneous injections.

The previously reported increased risk of diabetic ketoacidosis due to disconnection or malfunction of the pump is not reported in contemporary studies. People using CSII remain at increased risk of ketosis if the insulin delivery is interrupted for any reason.

We found no evidence regarding the effects of CSII use on long-term complications/outcomes. A limitation of the current evidence is the limited number of trials that examined current insulin regimens.

DEFINITION

The term diabetes mellitus encompasses a group of disorders characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects of insulin secretion, insulin action, or both. The WHO definition now recognises diabetes as a progressive disorder of glucose metabolism in which individuals may move between normoglycaemia, impaired glucose tolerance or impaired fasting glycaemia, and frank hyperglycaemia. Type 1 diabetes occurs when destruction of the pancreatic islet beta cells, usually attributable to an autoimmune process, causes the pancreas to produce too little insulin or none at all. Markers of autoimmune destruction (autoantibodies to islet cells, autoantibodies to insulin, or autoantibodies to both islet cells and insulin, and to glutamic acid decarboxylase) can be found in 85% to 90% of people with type 1 diabetes when hyperglycaemia is first detected. [1] The definition of type 1 diabetes also includes beta-cell destruction, in people prone to ketoacidosis, for which no specific cause can be found. However, it excludes those forms of beta-cell destruction for which a specific cause can be found (e.g., cystic fibrosis, pancreatitis, pancreatic cancer). [2] Type 2 diabetes results from defects in both insulin secretion and insulin action. Type 2 diabetes is not covered in this review. **Population:** For the purpose of this review, we have included adolescents and adults with type 1 diabetes, but have excluded pregnant women and people who are acutely unwell: for example, after surgery or MI.

INCIDENCE/ PREVALENCE

The prevalence of type 1 diabetes is 0.02% in people aged 0 to 14 years, and it is estimated that 479,000 people in this age group have type 1 diabetes worldwide, with annual increase in incidence of 3%. [3] Each year, 75,000 new cases are diagnosed in this age group. [3] Although type 1 diabetes usually accounts for only a minority of the total burden of diabetes in a population, in most resource-rich countries it is the predominant form of the disease in younger age groups. Nearly a quarter of people with diabetes come from the European region. [3] There is a worldwide increase in the incidence of childhood diabetes with age of onset shifting to a younger age group. [4] [5] This younger age at onset means that complications appear at a younger age, and dependence on lifelong insulin imposes a heavy burden on people as well as on health services.

AETIOLOGY/ RISK FACTORS

Two main aetiological forms of type 1 diabetes are recognised. Autoimmune diabetes mellitus results from autoimmune-mediated destruction of the beta cells of the pancreas. The rate of destruction varies, but all people with this form of diabetes eventually become dependent on insulin for survival. Peak incidence of autoimmune diabetes is during childhood and adolescence, but it may occur at any age. There is a genetic predisposition, and people with this type of diabetes may have other autoimmune disorders. [6] Certain viruses, including rubella, Coxsackie B, and cytomegalovirus, have been associated with beta-cell destruction. Other environmental factors are probably also contributory, but these are poorly defined and understood. Idiopathic diabetes (in which the cause is unidentified) is more common in individuals of African and Asian origin. [2]

PROGNOSIS

Untreated, most people with type 1 diabetes, particularly those with autoimmune diabetes mellitus, will experience increasing blood glucose levels, progressing to ketoacidosis resulting in coma and death. The course of idiopathic diabetes may be more varied, with some people experiencing permanent lack of insulin and a tendency to ketoacidosis, although in others the requirement for insulin treatment may fluctuate. [2] However, most people with type 1 diabetes require insulin for survival, and are described as insulin dependent. The long-term effects of diabetes include retinopathy, nephropathy, and neuropathy. People with diabetes mellitus are also at increased risk

of CVD, peripheral vascular disease, and cerebrovascular disease. Good glycaemic control can reduce the risk of developing diabetes-related complications. [7]

AIMS OF INTERVENTION

To control blood glucose levels; to maximise quality of life; to prevent diabetes-related emergencies, such as ketoacidosis; to maintain HbA1c levels at optimal level in order to slow disease progression and reduce risk of microvascular and macrovascular complications; to minimise adverse effects of treatment.

OUTCOMES

Mortality. **Long-term outcomes: microvascular**, such as development of retinopathy, nephropathy, and neuropathy, and **macrovascular**, such as CVD (including cardiac events, stroke, and peripheral vascular disease). **Glycaemic control:** change in glycated haemoglobin (e.g., as measured by HbA1c). **Quality of life**. **Adverse effects:** incidence of and mortality from hypoglycaemia; incidence of and mortality from diabetic ketoacidosis; weight gain; fluid retention; neuropsychological impairment; other adverse effects.

METHODS

Clinical Evidence search and appraisal February 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to February 2010, Embase 1980 to February 2010, and The Cochrane Database of Systematic Reviews 2010, Issue 1 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs, cohort studies, or RCTs and cohort studies, and RCTs in any language, containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies, apart from for HbA1c levels, where 3-month follow-up was required. We included studies described as "open", "open label", or not blinded. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. Measuring glycated haemoglobin using HbA1c is now the standard method for monitoring glycaemic control. We have therefore preferentially reported HbA1c as a measure of glycaemic control. However, some older studies do not report this measure, in which case we have reported the measure of glycaemic control used. Crossover trials were included only if results were reported at the end of the initial treatment period before crossover. Educational interventions are defined as interventions, single or multiple, that provide information, self-management programmes, or both. Interventions primarily focused on the organisational aspects of delivery of care have been excluded. Educational interventions for adults and adolescents have been considered separately, because adolescents are generally acknowledged to have different educational needs from adults, and poorer glycaemic control. Studies of intensive treatment programmes had to include multiple daily injections or the use of an insulin pump. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 22).The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of intensive treatment programmes, psychological interventions, and educational interventions in adults and adolescents with type 1 diabetes?**

OPTION INTENSIVE TREATMENT PROGRAMMES

Mortality

Compared with conventional treatment We don't know whether intensive treatment is more effective than conventional treatment at reducing mortality in adults with type 1 diabetes (low-quality evidence).

Long-term outcomes (microvascular)

Compared with conventional treatment Intensive treatment seems to be more effective than conventional treatment at reducing the risk of retinopathy or retinopathy progression, the risk of neuropathy, and the risk of microabuminuria

and albuminuria in adults with type 1 diabetes. Intensive treatment seems to be more effective than conventional treatment at reducing the risk of retinopathy and retinopathy progression in adolescents aged 13 to 17 years with type 1 diabetes (moderate-quality evidence).

Long-term outcomes (macrovascular)
Compared with conventional treatment Intensive treatment may be more effective than conventional treatment at reducing the proportion of people with a composite outcome of macrovascular events of any type (including fatal and non-fatal cardiac events, stroke, and peripheral vascular events) in adults with type 1 diabetes, but we don't know about adolescents (low-quality evidence).

Glycaemic control
Compared with conventional treatment Intensive treatment seems to be more effective than conventional treatment at reducing glycosylated haemoglobin levels (measured by HbA1c or other measures) in adults and adolescents with type 1 diabetes (moderate-quality evidence).

Adverse effects
Compared with conventional treatment Intensive treatment seems to be associated with an increase in severe hypoglycaemic events compared with conventional treatment in adults and adolescents with type 1 diabetes. Some studies found an increase in diabetic ketoacidosis associated with the use of insulin pumps; however, this was in older studies and was not reported in more contemporary studies using modern pumps (low-quality evidence).

For GRADE evaluation of interventions for diabetes: glycaemic control in type 1, see table, p 22 .

Benefits:

Intensive treatment programmes versus conventional treatment:
Adults
We found two systematic reviews. [8] [9] The second review included one large RCT (the Diabetes Control and Complications Trial [DCCT]), which was published as an initial report and a series of longer term follow-up reports. [7] [10] [11] [12] [13] [14] [15] [16]

The first review (search date 1991) included 16 RCTs and examined the effects of intensive blood glucose control on late complications of type 1 diabetes. [8] Most included RCTs were performed over 20 years ago (RCTs published between 1979 and 1991), and the duration of follow-up ranged from 8 to 60 months. Conventional control was achieved by one or two injections of insulin daily while intensive therapy was achieved by continuous subcutaneous insulin infusion (CSII) or by multiple injections. The review found that intensive therapy significantly reduced glycosylated haemoglobin compared with conventional control by the end of the study (glycosylated Hb: difference –1.4%, 95% CI –1.8% to –1.1%; absolute numbers and number of RCTs included in the analysis not reported). [8] Eight RCTs included people with retinopathy, usually non-proliferative or background in type. Six RCTs ranked or graded the level of retinopathy, and two RCTs used the number of microaneurysms to assess severity. The review found that intensive therapy significantly reduced the risk of retinopathy progression compared with conventional control after 2 to 5 years (6 RCTs, 271 people; OR 0.49, 95% CI 0.28 to 0.85; P = 0.011; absolute numbers not reported; results presented graphically). [8] The review found higher rates of retinopathy in the intensive group at 6 to 12 months, although differences between groups were not significant (OR 2.11, 95% CI 0.54 to 8.31; absolute numbers not reported), and there was significant heterogeneity among RCTs (P = 0.046). The progression of nephropathy was defined as an increment in urinary albumin excretion. Most studies included people with normal albumin excretion or microalbuminuria or normal serum creatinine. The review found that intensive therapy significantly reduced the risk of nephropathy progression compared with conventional control (7 RCTs, 266 people; OR 0.34, 95% CI 0.20 to 0.58; P <0001; absolute numbers not reported; results presented graphically). [8]

The second review (search date not reported, 7 RCTs [published between 1983 and 1993], 1800 people with 11,293 person-years of follow-up) examined the effects of intensive control on the incidence of new macrovascular complications (cardiac, cerebrovascular, and peripheral vascular disease). [9] The review included people with type 1 and 2 diabetes; we have only reported data pertaining to people with type 1 diabetes here. The review noted that study populations were heterogeneous, with a range of mean ages (26–42 years) and duration of diabetes (2.6–20 years) at baseline. It reported that intensified treatment typically consisted of multiple injection therapy or CSII using a pump, with intensive self-monitoring of blood glucose. Conventional treatment was based on one to three injections with or without occasional blood glucose monitoring. One large RCT (the DCCT) formed the majority of people included in the review (1441/1800 [80%]). The data from this RCT was analysed as two separate studies based on the presence or absence of baseline diabetic retinopathy (primary and secondary prevention arms). The review reported on macrovascular end points, which were defined as cardiac events (fatal and non-fatal MI, any type of bypass graft and PTCA, angina pectoris, congestive heart failure, and death from cardiac disease or sudden death); stroke (fatal and non-fatal, thrombotic or haemorrhagic); and peripheral vascular disease (including intermittent claudication, diabetes-related amputation of lower extremity, any type of

peripheral artery bypass or angioplasty, and death from peripheral arterial disease). The primary end point was the incidence of fatal or non-fatal macrovascular events of any type. At the conclusion of the studies, the difference in HbA1c between the intensive and conventional treatment groups ranged from –20.9 mmol/mol to –5.5 mmol/mol (–1.9% to –0.5%) in favour of the intensive group (further statistical analysis not reported). The review found that a total of 134 new macrovascular events of any type were reported. It found that intensive treatment significantly reduced the incidence rate ratio (IRR) of macrovascular events of any type compared with control (7 RCTs; IRR 0.38, 95% CI 0.26 to 0.56; absolute numbers not reported; results presented graphically). [9] In subgroup analysis by type of event, it found that, compared with control, intensive treatment significantly reduced the IRR of cardiac events and peripheral vascular events, but not of stroke (cardiac: 6 RCTs [40 events]; IRR 0.41, 95% CI 0.19 to 0.87; peripheral vascular events: 4 RCT [88 events]; IRR 0.39, 95% CI 0.25 to 0.62; stroke: 2 RCTs [6 events]; IRR 0.34, 95% CI 0.05 to 2.57; absolute numbers not reported; results presented graphically). [9] However, the stroke result was based on a small number of events (6 events in total). The review found no significant difference between groups in macrovascular deaths (9 deaths in total; IRR 0.89, 95% CI 0.27 to 2.98). [9] The review noted that people included in the RCTs may not be representative of people with diabetes type 1 in general. Included RCTs enrolled young people, most in their 20s or 30s, who were at low risk of macrovascular events. [9]

The large RCT included in the second review (the DCCT; 1441 people aged 13–39 years, consisting of 726 people with no retinopathy at baseline and insulin-dependent diabetes mellitus [IDDM] for 1–5 years [the primary prevention group] and 715 people with very mild to moderate non-proliferative retinopathy and IDDM for 1–15 years [the secondary intervention group], mean age 27 years, mean duration of follow-up 6.5 years) was designed to compare the effects of intensive versus conventional diabetes therapy on the development and progression of the early vascular and neurological complications of diabetes and reported on microvascular outcomes. [7] The intensive therapy regimen was designed to achieve blood glucose values as close to the normal range as possible with three or more daily insulin injections or treatment with an insulin pump. The dosage was adjusted according to the results of blood glucose self-monitoring (done at least 4 times daily), dietary intake, and anticipated exercise, in order to meet preset blood glucose targets. Conventional treatment consisted of one or two subcutaneous insulin injections daily, daily self-monitoring of urine or blood glucose, and education about diet and exercise. People in the intensive treatment programme were seen at the study centre every month, and contacted more frequently by telephone to review and adjust their treatment; people in the conventional treatment group were seen and examined every 3 months. The RCT found that, compared with conventional treatment, intensive treatment significantly reduced glycated haemoglobin (median of all quarterly HbA1 values: 53 mmol/mol [7%] with intensive treatment regimens *v* 75 mmol/mol [9%] with conventional treatment; results presented graphically; P <0.001). [7]

The RCT reported that in people in the primary prevention group who did not have retinopathy at baseline, intensive therapy significantly reduced the adjusted mean risk for the development of retinopathy compared with conventional treatment over a mean follow-up of 6 years (defined as a change of 3 steps or more on fundus photography: rate 1.2 per 100 patient-years with intensive *v* 4.7 per 100 patient-years with conventional; risk reduction 76%, 95% CI 62% to 85%). [7] In the secondary prevention group, intensive therapy significantly slowed the progression of retinopathy compared with conventional treatment over the study period (progression of retinopathy by 3 steps or more: rate 3.7 per 100 patient-years with intensive *v* 7.8 per 100 patient-years with conventional; risk reduction 54%, 95% CI 39% to 66%), and significantly reduced the development of proliferative or severe non-proliferative retinopathy and the rate of treatment with photocoagulation (severe proliferative or non-proliferative retinopathy; rate: 1.1 per 100 patient-years with intensive *v* 2.4 per 100 patient-years with conventional; risk reduction 47%, 95% CI 14% to 67%; P = 0.011; laser treatment rate: 0.9 per 100 patient-years with intensive *v* 2.3 per 100 patient-years with conventional; risk reduction 56%, 95% CI 26% to 74%; P = 0.002). The RCT reported that in people with pre-existing retinopathy, intensive control was associated with a transient deterioration of retinopathy (sustained progression of retinopathy by 3 steps or more) during the first year of the study, but by 36 months, cumulative incidence of retinopathy was lower in the intensive group than in the conventional group until the end of the study (results presented graphically). Clinical neuropathy was defined as abnormal neurological examination consistent with peripheral sensorimotor neuropathy plus either abnormal nerve conduction in at least two peripheral nerves or abnormal autonomic nerve testing. In people in the primary prevention group who did not have neuropathy at baseline, intensive treatment significantly reduced the appearance of neuropathy compared with conventional treatment at 5 years (rate: 3.1 per 100 patient-years with intensive *v* 9.8 per 100 patient-years with conventional; risk reduction 69%, 95% CI 24% to 87%; P = 0.006). Similarly, in the secondary prevention group, intensive therapy significantly reduced the appearance of clinical neuropathy compared with conventional treatment at 5 years (rate: 7.0 per 100 patient-years with intensive *v* 16.1 per 100 patient-years with conventional; risk reduction 57%, 95% CI 29% to 73%; P <0.001). Intensive treatment also significantly reduced neuropathy in both primary and secondary prevention

groups combined (risk reduction 60%, 95% CI 38% to 74%). In the two groups combined (primary and secondary prevention groups based on presence of baseline retinopathy), the RCT found that intensive therapy significantly reduced the occurrence of microalbuminuria (urinary albumin excretion of 40 mg per 24 hours or greater) compared with conventional treatment (risk reduction 39%, 95% CI 21% to 52%), and significantly reduced albuminuria (urinary albumin excretion 300 mg/24 hours or greater) compared with conventional treatment (risk reduction 54%, 95% CI 19% to 74%). [7]

Adolescents

The large RCT included in the second review (the DCCT) also included participants aged 13 to 17 years (195 adolescents in total, 125 adolescents with no retinopathy at baseline and IDDM for 1–5 years [the primary prevention group] and 70 adolescents with mild to moderate non-proliferative retinopathy and IDDM for 1–15 years [the secondary intervention group]), and results for adolescents at the time of study entry have been published separately. [15] Participants were randomly assigned to receive either intensive therapy or conventional therapy and were followed up for a mean of 7.4 years (range 4–9 years). Conventional therapy consisted of one or two daily insulin injections, once-daily self-monitoring of urinary or blood glucose values, and diet and exercise education. Intensive therapy consisted of insulin three or more times daily by injection or external pump, adjusted by dietary intake, anticipated exercise, or results of self-monitoring (see trial description above).

The RCT found that intensive treatment significantly decreased HbA1c levels compared with conventional treatment (results for study years 0–9 presented graphically; P <0.001). It reported that a substantial separation of HbA1c levels was seen by 6 to 12 months and this difference was maintained between the groups throughout the remainder of the trial. [15] The RCT reported that in the primary prevention group, intensive therapy significantly decreased the risk of having retinopathy compared with conventional treatment (3-step or greater progression: 3.2 per 100 patient-years with intensive *v* 6.3 per 100 patient-years with conventional; risk reduction 53%, 95% CI 1% to 78%; P = 0.048). [15] In the secondary intervention group, the RCT found that intensive therapy significantly decreased the risk of retinopathy progression compared with conventional treatment (3-step or greater progression: 2.9 per 100 patient-years with intensive *v* 7.4 per 100 patient-years with conventional; risk reduction 70%, 95% CI 25% to 88%; P = 0.010) and significantly decreased the occurrence of microalbuminuria (urinary albumin >40 mg in 24 hours: 6.6 per 100 patient-years with intensive *v* 12.7 per 100 patient-years with conventional; risk reduction 55%, 95% CI 3% to 79%; P = 0.042). The RCT found no significant difference between intensive and conventional treatment in reduction of microalbuminuria in the primary prevention group (risk reduction +10%, 95% CI –70% to +52%; P = 0.745). Only a small number of adolescents in either group had clinical grade albuminuria (9 people in total; reported as no significant difference between groups; P value not reported). The number of participants in whom clinical neuropathy developed was small and the treatment group differences were not significant (3 people with intensive *v* 7 people with conventional; reported as no significant difference; P value not reported). However, motor and sensory nerve conduction velocities were significantly slower in conventionally treated than in intensively treated adolescents at 5 years (median motor, P <0.003; median sensory, P = 0.04; peroneal, P <0.001; sural, P <0.004). [15]

Harms:

Intensive treatment programmes versus conventional treatment:

Adults

The first review reported that only 6 RCTs provided combinable data on severe hypoglycaemia. [8] The review found no significant difference between groups in severe hypoglycaemic reactions, although rates were higher among intensively treated people (6 RCTs; difference +9.1 episodes per 100 person-years, 95% CI –1.4 episodes per 100 person-years to +19.6 episodes per 100 person-years; absolute numbers not reported). The review found that the incidence of diabetic ketoacidosis was significantly higher in people treated with continuous subcutaneous insulin infusion (CSII) than in those treated conventionally (3 RCTs; difference 12.6 episodes per 100 person-years, 95% CI 8.7 episodes per 100 person-years to 16.5 episodes per 100 person-years; absolute numbers not reported). [8] Data on diabetic ketoacidosis were not provided in people treated with multiple injections. It should be noted that RCTs included in the analysis were old (published before 1991) and such an increase in rate of diabetic ketoacidosis was not seen in more recent trials of insulin pump therapy (see harms of continuous subcutaneous insulin infusion compared with multiple daily subcutaneous insulin injection, p 16).

The second review did not report on harms. [9]

The large RCT (the DCCT) included in the second review reported on adverse effects. [7] The RCT found that intensive treatment significantly increased the occurrence of severe hypoglycaemia compared with conventional treatment (severe hypoglycaemia in which assistance was required in the provision of treatment: 62 episodes per 100 patient-years with intensive treatment *v* 19 episodes per 100 patient-years with control treatment; P <0.001). The RCT reported that this included 16 episodes of coma or seizure per 100 patient-years in the intensive group and 5 episodes

of coma or seizure per 100 patient-years in the conventional group (statistical analysis between groups not reported). The RCT reported that there were two fatal motor vehicle accidents, one in each group, in which hypoglycaemia may have had a causative role. The RCT found no significant difference between intensive and conventional treatment in diabetic ketoacidosis (2.0 episodes per 100 patient-years with intensive treatment *v* 1.8 episodes per 100 patient-years with conventional treatment; P >0.7). [7] Over a 9-year study period, the RCT found an excess weight gain of 4.75 kg with intensive treatment compared with conventional treatment, with about half the excess weight gain occurring in the first year (3.3 kg weight gain with intensive treatment *v* 1.2 kg weight gain with control treatment; P <0.0001). [17]

We found a further systematic review (search date 1995, 14 RCTs, 1028 adults with intensive treatment and 1039 adults with conventional treatment), which included the DCCT above, and which conducted a meta-analysis of adverse effects of intensive treatment in people with type 1 diabetes. [18] The review found that, compared with conventional treatment, intensive treatment significantly increased the risk of hypoglycaemia (1 or more episodes of severe hypoglycaemia: 14 RCTs, 2067 people; OR 2.99, 95% CI 2.45 to 3.64; P <0.0001). It also found that intensive treatment significantly increased the risk of diabetic ketoacidosis compared with conventional treatment (14 RCTs, 2067 people; OR 1.74, 95% CI 1.27 to 2.38; P = 0.0003), but this was largely because of an increased risk of diabetic ketoacidosis in those RCTs involving intensive treatment with insulin pumps. It should be noted that RCTs included in the analysis were old (published between 1983 and 1995) and such an increase in rate of diabetic ketoacidosis was not seen in more recent trials of insulin pump therapy (see harms of continuous subcutaneous insulin infusion compared with multiple daily subcutaneous insulin injection, p 16). The review found no significant difference in the incidence of diabetic ketoacidosis between intensive treatment and conventional treatment in RCTs involving multiple insulin injections (1 RCT; OR 1.13, 95% CI 0.15 to 8.35; P = 0.09). The review noted that this result was based on one RCT, but there were three additional RCTs with no events both in people treated with multiple daily injections and people treated with conventional treatment. The review found no significant difference between groups in all-cause mortality (14 RCTs, 2067 people; OR 1.40, 95% CI 0.65 to 3.02; P = 0.39). [18]

For adverse effects of insulin pumps, see harms of continuous subcutaneous insulin infusion compared with multiple daily subcutaneous insulin injection, p 16 .

Adolescents:
The large RCT (DCCT) included in the second review found that, similar to the overall analysis of all people in the RCT, that people aged 13 to 17 years experienced a nearly threefold increase in episodes of severe hypoglycaemia with intensive treatment than with conventional control (all severe hypoglycaemic events requiring assistance; rate: 85.7 events per 100 patient-years with intensive treatment *v* 27.8 events with conventional treatment; RR 2.96, 95% CI 1.90 to 4.62; P <0.001). [15] These events included 26.7 episodes per 100 patient-years of coma or seizure with intensive treatment and 9.7 episodes per 100 patient-years of coma or seizure with conventional treatment (RR 2.93, 95% CI 1.75 to 4.90; P <0.001). The RCT found that there was no significant difference between groups in the event rates for diabetic ketoacidosis (2.8 episodes per 100 patient-years with intensive treatment *v* 4.7 episodes per 100 patient-years with conventional treatment; RR 0.62, 95% CI 0.32 to 1.23; P = 0.174). [15]

Comment:

Clinical guide:
The RCT (Diabetes Control and Complications Trial [DCCT]) included in the second review is widely accepted as the "gold standard" RCT demonstrating that tight glycaemic control is of long-term benefit in people with type 1 diabetes. [7] Patients in the intensive group also received frequent follow-up and blood glucose monitoring — meaning that improvements in glycaemic control cannot be attributed solely to the effects of intensified insulin treatment. Most intensive interventions to improve glycaemic control are likely to involve modification of treatment, as well as patient education and training in self-management. The most notable drawback of intensification of treatment is increased risk of hypoglycaemia with a threefold increase in incidence of severe hypoglycaemia in the intensive arm of the DCCT. However, during the DCCT, there was no formal structured patient education programme, and insulins used in multiple daily injection or continuous subcutaneous insulin injection (CSII) in the intensively treated group were human insulins rather than modern insulin analogue. The DCCT did not find any difference in quality of life for intensively treated people compared with those receiving conventional treatment.

There have been several observational studies originating from the DCCT that have looked at long-term effects (so-called "legacy effect" or "metabolic memory") of intensive treatment. Data from the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study, a long-term follow-up report of the DCCT, suggest that intensive diabetes treatment has long-term beneficial effects on the risk of CVD. [10] At the end of the DCCT, the conventional treatment group was offered intensive treatment, and all participants returned to their own healthcare providers for dia-

betes care. During the mean 17 years of follow-up, the EDIC study found that intensive treatment reduced the risk of any CVD events by 42%, and the risk of non-fatal MI, stroke, or death from CVD by 57%. [10] Data from the same follow-up study found that, 6.5 years after the DCCT, the former intensive group of the DCCT had a significantly lower prevalence of neuropathy compared with the conventional group, based on a positive questionnaire (neuropathy assessed by Michigan Neuropathy Screening Instrument: 1.8% with intensive *v* 4.7% with conventional; P = 0.003) or based on clinical examination (18% with intensive *v* 28% with conventional; P <0.0001). [11] Further studies have found a 59% reduction in the odds for development of new cases of microalbuminuria after 7 to 8 years, [12] a 31% reduction of the risks of incident cardiac autonomic neuropathy after 13 to 14 years, [13] and a 24% reduction of the risk of incident hypertension after 15 years [14] in people assigned to the intensive arm of the DCCT. Similar long-term benefits in the intensive treatment group of the adolescent group were also seen with regards to worsening of retinopathy and of progression to proliferative or severe non-proliferative retinopathy after 4 years of follow-up at the end of the DCCT. [16]

One of the main challenges of contemporary diabetes care is to achieve tight glycaemic control without increasing the risk of hypoglycaemia. Structured patient education, modern insulin analogues, insulin pump therapy, and continuous glucose monitoring could all be valuable tools in reducing the risk of hypoglycaemia in an individual person. There is a need for further studies to improve our understanding of how best to combine these therapeutic options, and to demonstrate that tight glycaemic control could be achieved without increasing the risk of hypoglycaemia.

OPTION EDUCATIONAL INTERVENTIONS

Glycaemic control
Compared with usual care/control Immediate insulin dose adjustment training to enable dietary freedom (Dose Adjustment for Normal Eating [DAFNE] training) may be more effective than waiting list control at improving HbA1c levels at 6 and 12 months in adults with type 1 diabetes, but we don't know about other educational interventions. We don't know whether educational interventions are more effective than control at reducing glycated haemoglobin in adolescents (mean age range 9–14.5 years) with type 1 diabetes (low-quality evidence).

Quality of life
Compared with usual care/control Immediate insulin dose adjustment training to enable dietary freedom (DAFNE training) may be more effective at improving quality of life (measured by Diabetes Quality Of Life [DQOL]) at 6 months in adults with type 1 diabetes, but we don't know about other educational interventions. Educational interventions may be more effective than control at improving some psychosocial outcomes (including quality of life measures) in adolescents with type 1 diabetes (very low-quality evidence).

For GRADE evaluation of interventions for diabetes: glycaemic control in type 1, see table, p 22 .

Benefits:

Educational interventions versus usual care/control:
Adults
We found one systematic review (search date 2002), [19] which identified one RCT, [20] and two subsequent RCTs of education for individuals. [21] [22]

The RCT identified by the review found no significant difference in HbA1c levels at 18 months between education in self-monitoring of blood glucose, self-management education, or usual care (1 RCT, 37 adults, aged over 17 years, attending an outpatient clinic; mean reduction in HbA1c: 23.1 mmol/mol [2.1%] with education plus blood glucose self-monitoring *v* 22.0 mmol/mol [2.0%] with blood glucose self-monitoring alone *v* 22.0 mmol/mol [2.0%] with education alone *v* 8.8 mmol/mol [0.8%] with usual care; reported as "did not differ significantly between any of the groups"; P value not reported). [20] The RCT was incompletely reported, and may have been underpowered to detect clinically important differences. [20]

The first subsequent RCT compared immediate insulin dose adjustment training to enable dietary freedom ([Dose Adjustment for Normal Eating [DAFNE] training) versus a waiting list control group attending insulin dose adjustment training 6 months later. [21] DAFNE training consisted of a 5-day training course providing people with the skills to match insulin dose to desired carbohydrate intake on a meal-by-meal basis. The RCT found that, compared with delayed training in insulin dose adjustment to enable dietary freedom, immediate insulin dose adjustment training significantly improved HbA1c levels and led to a small improvement in diabetes-dependent quality of life at 6 months, which was maintained at 1 year (1 RCT, 169 adults with type 1 diabetes and moderate or poor glycaemic control defined as HbA1c 59–106 mmol/mol [7.5–12%], mean age 40 years; improvement in HbA1c at 6 months: mean difference between groups 11 mmol/mol, 95% CI 5.5 mmol/mol to 15.4 mmol/mol [1.0%, 95% CI 0.5% to 1.4%]; P <0.0001; improvement in HbA1c at 12 months: mean difference between groups 5.5 mmol/mol, 95% CI 2.5 mmol/mol to 9.9 mmol/mol [0.5%, 95% CI 0.2% to 0.9%]; P = 0.001; mean difference between groups in Diabetes Quality Of Life [DQOL]

scale at 6 months: +0.4, 95% CI –0.1 to +0.9; P <0.01; at 12 months: quantitative values not reported; on the DQOL scale, possible scores range from –9 = maximum negative impact of diabetes to +9 = maximum positive impact of diabetes). [21]

The second subsequent RCT (117 people, mean age 41 years, duration of diabetes about 19 years) compared the effectiveness of a brief (2.5 days) educational intervention (Brief Intervention in Type 1 diabetes, Education for Self-efficacy; BITES) versus usual clinic-based diabetes care. [22] The study intervention was delivered over a 6-week period facilitated by a specially trained diabetes nurse and a specialist diabetes dietician in 6 groups of 8 to 10 participants and covered three educational themes: understanding carbohydrates and diet; understanding insulin adjustment; and giving people skills and confidence to self-manage diabetes. In addition to providing skills training to match insulin to carbohydrate content, the study intervention also included the use of some cognitive behavioural techniques. This is by contrast with two previously reported RCTs, in which no such psychological component was included (for interventions that are predominantly psychological in nature, see psychological interventions, p 10). The RCT found no significant difference between the BITES intervention and usual care in HbA1c at 3 months (difference +0.11 mmol/mol, 95% CI –2.2 mmol/mol to +2.3 mmol/mol [+0.01%, 95% CI –0.23% to +0.26%]; P = 0.92), at 6 months (difference –0.66 mmol/mol, 95% CI –3.4 mmol/mol to +2.2 mmol/mol [–0.06%, 95% CI –0.32% to +0.20%]; P = 0.67), or at 12 months (difference +0.11 mmol/mol, 95% CI –3.3 mmol/mol to +3.4 mmol/mol [+0.01, 95% CI –0.30 to +0.32]; P = 0.94). Some quality of life indicators such as "treatment satisfaction", "managing psychological aspects", and "setting and achieving goals" improved with the BITES intervention compared with usual care, although there was no significant difference between groups in short form-36 physical health or mental health scores at 3, 6, or 12 months (all P values > 0.05). [22]

Adolescents

We found one systematic review (search date 1999), [23] which evaluated the effects of different educational and psychosocial interventions in adolescents with type 1 diabetes. The systematic review included studies using different measurements for glycated haemoglobin levels and quality of life. [23] Most of the RCTs identified by this systematic review were small studies, lacking sufficient power to detect small to medium effect sizes. They were characterised by a wide variety of interventions and a lack of standardised or validated outcome measures. The control groups in the analysis included usual care, no intervention, an intensive management group without coping skills training (compared with intensive management group with skills training), and a game to play with no health message (compared with a game to play with a diabetes health message). The authors of this review conducted meta-analyses using effect sizes giving a pure number free of the original measurement unit. The authors stated that, in the behavioural sciences, effect sizes of about 0.2 would be considered small, 0.5 to be medium, and those >0.8 to be large. The review reported psychosocial outcomes, which included quality of life, but also other outcome measures including self-efficacy for diabetes, measures of family climate or conflict, and diabetes-specific stress. The review found that, compared with controls, educational interventions produced a small improvement in psychosocial outcomes (8 RCTs, data on total number of people and age range not available; mean effect size 0.37, 95% CI 0.19 to 0.55). The review also found that, compared with controls, educational interventions reduced glycated haemoglobin (12 RCTs, 573 adolescents, mean age range 9.0–14.5 years; mean effect size +0.33, 95% CI –0.04 to +0.70, equivalent to a reduction in HbA1c of 6.6 mmol/mol [0.6%]; P value not reported). [23] There was significant statistical heterogeneity between included RCTs. A sensitivity analysis removing two large RCTs found a smaller effect size (mean effect size +0.08, 95% CI –0.10 to +0.26).

Harms:

Educational interventions versus usual care/control:

Adults

The RCT identified by the systematic review [19] did not report any data on the incidence of hypoglycaemia, diabetic ketoacidosis, or all-cause mortality for education in self-monitoring of blood glucose, self-management education, or usual care. [20] The first subsequent RCT comparing immediate insulin dose adjustment training to enable dietary freedom (DAFNE training) versus a waiting list control group attending insulin dose adjustment training 6 months later found no significant difference between the two groups in the perceived frequency of hypoglycaemia (1 RCT, 169 adults with type 1 diabetes and moderate or poor glycaemic control defined as HbA1c 59 mmol/mol to 106 mmol/mol [7.5% to 12.0%], mean age 40 years; mean difference in perceived hypoglycaemia score –0.23, 95% CI –0.68 to +0.21; P = 0.31, on a scale of 0–6, where higher scores indicate a higher perceived frequency of hypoglycaemia). [21] This RCT did not report on other outcomes of interest. The second subsequent RCT found no significant difference between groups in severe hypoglycaemia at 12 months (severe episodes per participant per year: 0.41 with educational intervention *v* 0.48 with control; difference –0.05, 95% CI –0.61 to +0.50; P = 0.85). [22] We found one further follow-up of an RCT of a cohort of 636 people who had participated in a 5-day structured inpatient diabetes education programme, which found a significant reduction in HbA1c and risks of severe hypoglycaemic episodes after 6 years compared with baseline (baseline to 6 years: mean

HbA1c, 67 mmol/mol to 60 mmol/mol [8.3% to 7.6%]; P <0.001; severe hypoglycaemia, 0.28 cases/person/year to 0.17 cases/person/year; P <0.05). [24]

Adolescents
The systematic review gave no information on adverse effects. [23]

Comment:

Clinical guide:
General: Structured patient-education programmes are pivotal to achieving tight glycaemic control with an acceptable amount of hypoglycaemia. However, there is a dearth of high-quality published studies, and all the RCTs cited are based upon the Diabetes Teaching and Training Programme, which was developed in Düsseldorf (including Dose Adjustment for Normal Eating [DAFNE]). These programmes are characterised by a set curriculum, a trained healthcare delivery team, and adult learning principles, with a robust quality assurance, including educator peer review and audit. The curriculum is based on carbohydrate counting, and on a basal bolus insulin regimen. At present, there is no uniform follow-up programme after attendance on a DAFNE course, and it would be helpful to have an RCT looking at the impact of structured DAFNE follow-up. The follow-up of an RCT suggested some slippage in glycaemic control by 6 years, [24] and it is likely that a skills-maintenance programme is required following initial attendance on a DAFNE course. In the UK, the Department of Health has recommended that every Primary Care Trust offers structured education for people with type 1 diabetes. Department of Health and NICE guidelines mention that the DAFNE may be a suitable structured education model. [25] [26]

OPTION PSYCHOLOGICAL INTERVENTIONS New

Glycaemic control
Compared with control We don't know whether psychological interventions are more effective than control at improving glycaemic control in adults and adolescents with type 1 diabetes. However, evidence was weak and results varied by the specific intervention used (very low-quality evidence).

Quality of life
Compared with control Psychological interventions may be more effective than control at improving some psychological outcome measures in adults and adolescents with type 1 diabetes. However, evidence was very weak, inconsistent, varied by the specific intervention used, and also varied by the specific outcome measures used (very low-quality evidence).

For GRADE evaluation of interventions for diabetes: glycaemic control in type 1, see table, p 22 .

Benefits:

Psychological interventions versus control:
Adults
We found one systematic review [27] and 5 subsequent RCTs in 6 reports [28] [29] [30] [31] [32] [33] looking at a variety of psychological interventions in adults with type 1 diabetes.

The systematic review (search date 2004) included RCTs in children/adolescents or adults with type 1 diabetes that evaluated the effect of psychological interventions on long-term glycaemic control (including HbA1c, HbA1, and glycated haemoglobin measurements made by different methods) and a continuous measure of psychological distress. [27] We have only reported data on adults here. The review included both published and unpublished RCTs, and categorised psychological interventions into 4 groups: supportive or counselling therapy, CBT, psychoanalytically informed therapies, and family systems therapy. Delivery was defined as individual, group, or family, and the review included RCTs where the control group was non-psychological (usual care, education, attention control, waiting list). The review identified 13 RCTs in adults. All but two RCTs had sample sizes <100 people. Participants included people with suboptimal glycaemic control, new onset diabetes, complications, and obesity, and the interventions included CBT (9 RCTs), psychoanalytical techniques (2 RCTs), and counselling (2 RCTs). The mean duration of diabetes was 14.1 years with a mean follow-up of 7.2 months. The review found no significant difference between psychological interventions and control in the percentage of glycated haemoglobin (standardised effect size: 11 RCTs, 516 people; effect size –0.17, 95% CI –0.45 to +0.10; absolute reduction in glycated haemoglobin: +0.22%, 95% CI –0.13% to +0.56%). There was significant heterogeneity among RCTs in the analysis (P = 0.002). The review did not explain the heterogeneity. As part of a sensitivity analysis restricting the psychological intervention to group CBT, the review found no significant difference between groups in the percentage of glycated haemoglobin (standardised effect size +0.02, 95% CI –0.41 to +0.44; P = 0.95; absolute numbers not reported). The review found no significant difference between groups in measures of psychological distress (6 RCTs; standardised effect size –0.25, 95% CI –0.51 to +0.01; absolute numbers not reported). [27]

The first subsequent RCT (94 people, mean age 41.2 years, mean HbA1c 70 mmol/mol [8.5%], type 1 diabetes for at least 2 years) compared a CBT-based intervention versus control in people

with poorly controlled diabetes. [28] CBT was delivered mainly in the group format, combined with elements of necessary individualisation. A structured manual, incorporating all the sessions, was developed. The CBT intervention consisted of a basic intervention programme (weeks 0–8), where the main purpose was to map the participants' own behaviours using a logbook of daily self-register, and teach them different tools suitable for working towards behaviour change, as well as a structured maintenance programme (weeks 9–48), where the main focus was on maintaining the behaviour changes achieved and on tackling future risk of relapses. The control group had initial assessments and information on continuous glucose monitoring, but otherwise received usual care. The RCT reported that the psychological intervention significantly improved HbA1c compared with control at all time points over the course of the study (HbA1c levels based on adjusted means; 8 weeks: difference –7.2 mmol/mol, 95% CI –10.8 mmol/mol to –3.9 mmol/mol [–0.67%, 95% CI –0.97% to –0.36%]; 24 weeks: difference –10.3 mmol/mol, 95% CI –5.6 mmol/mol to –14.9 mmol/mol [–0.94%, 95% CI –1.36% to –0.51%]; 48 weeks: difference –5.4 mmol/mol, 95% CI –9.6 mmol/mol to –1.2 mmol/mol [–0.49%, 95% CI –0.87% to –0.11%]). The RCT reported that the psychological intervention significantly improved wellbeing ($P < 0.05$), diabetes-related distress ($P < 0.01$), perceived stress, anxiety, and depression (all $P < 0.05$). It is important to note that only 32% of the eligible patients screened agreed to participate in this study. Although 94 people were randomised, baseline data were reported for 74 people, 69 people completed the intervention at 48 weeks, and results were based on 74/94 (79%) people initially randomised. [28] Hence, results should be viewed with caution.

The second subsequent RCT compared nurse-delivered motivational therapy plus usual care, motivational therapy plus CBT plus usual care, and usual care alone. [29] The RCT included 344 adults with at least a 2-year history of type 1 diabetes (average baseline HbA1c, 80 mmol/mol [9.4%]). A diabetes-specific motivational enhancement therapy manual was developed and the participants were offered 4 individual face-to-face sessions of 50 minutes each. For people in the CBT arm, this was followed by 8 sessions of CBT over 4 months. The primary outcome was change in HbA1c at 1 year, and the RCT performed an intention-to-treat analysis. The RCT found that motivational therapy plus CBT significantly improved HbA1c compared with usual care at 1 year (HbA1c, estimated mean difference –5.0 mmol/mol, 95% CI –8.9 mmol/mol to –1.2 mmol/mol [–0.46%, 95% CI –0.81% to –0.11%]). It found no significant difference between motivational therapy alone and usual care at 1 year (HbA1c, estimated mean difference –2.1 mmol/mol, 95% CI –5.8 mmol/mol to +1.7 mmol/mol [–0.19%, 95% CI –0.53% to +0.16%]). It found no significant difference between either intervention group and usual care in diabetes quality of life score (satisfaction subscale [range 1–5]: motivational therapy plus CBT *v* usual care, mean difference +0.04, 95% CI –0.10 to +0.18; motivational therapy alone *v* usual care, mean difference –0.08, 95% CI –0.20 to +0.05). [29]

The third subsequent RCT (107 people) compared CBT versus blood glucose awareness training (BGAT) in people with poorly controlled type 1 diabetes. [30] Eighty-six people with HbA1c of 64 mmol/mol (8%) or more were analysed who had a mean duration of diabetes of 18 years. The RCT reported that between 6 and 12 months' follow-up, no significant changes were observed in HbA1c in either group (further numerical details and statistical analysis not reported). It found no significant difference between groups in psychological outcomes (Problem Areas In Diabetes scale [PAID], $P = 0.99$ at 6 months, $P = 0.68$ at 12 months; Centre for Epidemiological Studies–Depression scale [CES-D], $P = 0.74$ at 6 months, $P = 0.19$ at 12 months; Confidence in Diabetes Self-care scale [CIDS], $P = 0.73$ at 6 months, $P = 0.30$ at 12 months). [30] These results were based on 86/107 (80%) of people initially randomised. An earlier report of this RCT had reported outcomes at 3 months. [32] The RCT found that HbA1c was significantly reduced in the CBT group compared with the control group at 3 months ($P = 0.03$), but found no significant difference between groups in psychological outcomes (PAID, $P = 0.79$; CES-D, $P = 0.76$; CIDS, $P = 0.95$). [32]

The fourth subsequent RCT (138 people) compared BGAT versus a self-help control. [31] The BGAT training was delivered by a physician–psychologist team to groups of 5 to 12 people in 8 sessions at weekly intervals, focusing on internal clues, disruptions in cognitive and motor performance, and mood changes, as well as exogenous factors such as previous insulin injections, food consumption, and physical exercise. The self-help group was guided by one physician and 5 to 12 participants had three monthly sessions. The RCT found no significant difference between BGAT and control in HbA1c ($P = 0.94$). [31] Results were based on 103/138 (75%) people initially randomised.

The fifth subsequent RCT (32 people, HbA1c 105 mmol/mol [11.9%]) compared the effects of cognitive analytic therapy (CAT; 16 sessions) versus control (diabetes specialist nurse education; 14–18 sessions). [33] In total, 26/32 (81%) people completed the trial. The RCT found no significant difference between groups in mean HbA1 values at the end of the intervention ($P = 0.60$), 3 months after the intervention ($P = 0.98$), or 9 months after the intervention ($P = 0.20$). The RCT found no significant differences between groups at the end of treatment, at 3 months, or at 9 months, in

mean diabetes knowledge values (based on Charing Cross Diabetes Knowledge questionnaire) or psychological issues (measured by Inventory of Interpersonal Problems and semi-structured interview; all P values >0.05). [33] Of an initial 50 people who were asked to take part in the study, 32 (64%) accepted.

Adolescents

It should be noted that some educational interventions also include a psychological component (see educational interventions, p 8).

The systematic review reported above, which reported data on children, adolescents, and adults, did not report data for adolescents alone. [27] We have therefore not reported it further here.

We found one further systematic review (search date 1999) [23] and 6 subsequent RCTs in 7 reports [34] [35] [36] [37] [38] [39] [40] looking at a variety of psychological interventions in adolescents with type 1 diabetes. We have previously discussed the systematic review [23] under educational interventions, p 8 , as this review combined both educational and psychological interventions. It should be noted that some educational interventions also include a psychological component. In this section we have reported those interventions that are predominantly psychological in character.

The first subsequent RCT (81 people, aged 11–16 years, mean duration of diabetes 7.7 years) compared a diabetes personal trainer intervention (consisting of 6 self-monitoring, goal-setting, and problem-solving sessions with trained non-professionals; 41 people) versus usual care (40 people) and reported long-term outcomes at 2 years. [34] Randomisation was stratified by age (11–13 years or 14–16 years) and by diabetic control (HbA1c <64 mmol/mol [<8.0%] or >64 mmol/mol [>8.0%]). In the intervention group, a structured problem-solving process based on the principles of motivational interviewing and applied behavioural analysis was used to improve areas of diabetes management difficulty identified by the participants. Trained professionals conducted 6 in-person semi-structured sessions over a 2-month period. These sessions were supplemented by telephone calls. The RCT found that the psychological intervention significantly improved HbA1c compared with usual care at 2 years (68 mmol/mol [8.43%] with intervention *v* 74 mmol/mol [8.93%] with control; P = 0.05; ANCOVA adjusted for age and baseline HbA1c). Subgroup analysis by age revealed a greater effect among older rather than younger people (ages 11–13 years, 40 people; reported as not significant; P value not reported; age 14–16 years, 38 people; 8.46% with intervention *v* 9.61% with control; P = 0.011). [34]

The second subsequent RCT evaluated the revised Behavioural Family Systems Therapy for Diabetes (BFST-D) intervention on parent–adolescent communication. [35] BFST-D included problem-solving training, cognitive restructuring, communication training, and functional-structural family therapy. Families of 104 adolescent patients with diabetes were randomised to one of three groups for 6 months: standard care, an educational support group (usual care plus 12 multifamily sessions for education and social support), or BFST-D (12 sessions). The RCT found that BFST-D was significantly superior to standard care (10 of 12 comparisons) and the educational support group (6 of 12 comparisons) at improving the quality of family interaction. Also, improved individual communication between adolescents and mothers was noted with BFST-D. However, a similar change was not noted with fathers. There were no significant differences between groups in adherence or family conflict. The RCT did not directly compare changes in HbA1c between groups. [35]

The third subsequent RCT (91 adolescents, mean age about 14.8 years, duration of diabetes 6.2–7.2 years, HbA1c 71–73 mmol/mol [8.6–8.8%]) examined the impact of a health-related quality of life (HRQoL) intervention compared with usual care on the behavioural outcome of adolescent type 1 diabetes patients. [36] The HRQoL intervention included monitoring the HRQoL right before the 3-month appointment with the clinician and discussion of the HRQoL scores with the teenager during the appointment. The Child Health Questionnaire was used to assess physical and psychosocial wellbeing. When followed up at 1 year, participants in the HRQoL group reported significantly fewer behavioural problems, improved self-esteem and mental health, and increased participation in family activities. However, these were baseline analyses. The RCT reported that "no differences over time between the two groups on Physical Health, family conflicts (Diabetes-Specific Family Conflict Scale [DFCS]), or depression (CES-D) were observed". The RCT found no significant difference between groups in HbA1c levels (69 mmol/mol [8.4%] with HRQoL intervention *v* 68 mmol/mol [8.3%] with control; P = 0.54). [36]

The fourth subsequent RCT studied the impact of multi-systemic therapy on adolescents with poorly controlled diabetes [37] and included a follow-up report. [38] A total of 127 adolescents (aged 10–17 years, mean age 13.2 years, HbA1c 95.0–95.7 mmol/mol [11.03–11.69%] depending on group) with type 1 diabetes for at least 1 year were randomised to multi-systemic therapy (6 months of home and community-based psychotherapy plus standard care; 64 people) or a control group (standard care only; 63 people). Therapy was targeted at adherence-related problems within the

family and broader community systems. All families received quarterly visits from a multidisciplinary diabetes team. Hospital admission rates were analysed at 6-monthly intervals for 2 years. The RCT found no significant difference between groups in HbA1c (–7.3 mmol/mol [–0.68%] with intervention *v* 1.0 mmol/mol [+0.09%] with control; P <0.10). In a subgroup analysis by whether the participant was in a single- or two-parent home, the RCT found that glycaemic control was not significantly improved in two-parent homes (P value not reported), but was significantly improved in single-parent homes (P = 0.03). [37] The RCT found no significant difference between groups in family relationships (Family Relationship Index: 0.16 with intervention *v* 0.09 with control; reported as not significant; P value not reported). In subgroup analysis, the RCT reported that the intervention improved family relationships in adolescents in two-parent families (P = 0.01) but not in single-parent families (P = 0.18). [37] A follow-up report of the RCT found that multi-systemic therapy significantly reduced hospital admissions for diabetic ketoacidosis compared with control over 2 years (P = 0.019; absolute numbers not reported; results presented graphically). [38]

The fifth subsequent small RCT (31 people, mean age 13.5–14.2 years, glycohaemoglobin 17.0–17.4%) compared multi-systemic therapy versus standard care, and found that the intervention significantly reduced the number of inpatient admissions (P <0.01), but found no significant difference between the groups in the number of emergency room visits (reported as not significant; P value not reported). [39] It did not report on other outcomes of interest.

The sixth subsequent RCT (80 people, mean age about 15.4 years, mean duration of diabetes about 9.1 years) compared motivational interviewing versus control in teenagers with type 1 diabetes. [40] Motivational interviewing used the "menu of strategies" approach eliciting views and then exploring discrepancies between beliefs and behaviour. To control for the effect of additional contact, the control group received support visits. The RCT found that the psychological intervention significantly improved HbA1c levels at 1 and 2 years (1 year, P = 0.04; 2 years, P = 0.003). However, these data were based on 47/80 (59%) people initially randomised who had complete data. The RCT reported that the patterns of change were similar to those seen when all participants' data, including those with incomplete data, were analysed, but it did not present any further data. Hence, these results should be interpreted with caution. The RCT found that some of the secondary outcomes measured, such as positive wellbeing (measured by Well-Being Questionnaire [WBQ], P <0.001), quality of life (measured by DQOLY, P <0.001), and differences in personal models of illness (measured by Personal Models of Diabetes Questionnaire [PMDQ], P <0.001), were significantly improved at 12 months in the intervention group compared with the control group. [40]

Harms:

Psychological interventions versus control:

Adults

The review did not report on adverse effects. [27] The first subsequent RCT found that the CBT-based intervention significantly increased the incidence of hypoglycaemia compared with control at 24 and 48 weeks (measured by Diabetes Self Care Inventory; 24 weeks: difference 2.33, 95% CI 0.46 to 4.21; 48 weeks: difference 2.34, 95% CI 0.01 to 4.66; units not reported). [28] It reported that no participants reported severe hypoglycaemia requiring hospital admission, and that one episode of ketoacidosis requiring hospital admission occurred in the intervention group. [28] The second subsequent RCT found no significant difference between either intervention group and usual care in the estimated mean number of severe hypoglycaemia events at 1 year, although rates were lower in the intervention groups (estimated mean number of reported events lower in intervention groups compared with usual care group: motivational enhancement plus CBT +0.62, 95% CI –0.38 to +1.61; motivational enhancement alone +0.79, 95% CI –0.17 to +1.76). [29] It found no significant difference between either intervention group and usual care in body mass index. [29] The third subsequent RCT did not report on harms. [30] The fourth subsequent RCT found that BGAT significantly reduced severe hypoglycaemia at 6 months (P = 0.04) and fear of hypoglycaemia (P = 0.02) compared with self-help control. [31] The fifth subsequent RCT did not report on adverse effects. [33]

Adolescents

The first, second, third, fifth, and sixth subsequent RCTs did not report on harms. [34] [35] [36] [39] [40] The fourth subsequent RCT reported on prevention of diabetic ketoacidosis (see benefits above), but did not report on other adverse effects. [38]

Comment:

The available studies evaluating psychological interventions aimed at improving glycaemic control in type 1 diabetes have several design limitations. Low study enrolment rates and high withdrawal rates have limited the sample size and the overall quality of the studies, both in adults and adolescents. Furthermore, some of the studies used usual diabetes care as a comparator. It is unclear what proportion of improvement is attributable to the psychological intervention per se or what improvement is attributable to the increased contact with healthcare professionals.

Of the many psychological interventions that have been trialled, CBT seems to be superior, but the improvements in HbA1c were only modest and remained above the targets for good control in most studies. In adolescents, interventions aimed at improving family relationships were associated with improvements in glycaemic control and in quality of life. Larger and longer randomised studies with effective comparator arms may be needed to study the sustainability of the improvement caused by psychological interventions in glycaemic control and over all quality of life outcomes among people with type 1 diabetes mellitus.

QUESTION **What are the effects of different insulin regimens or frequency of blood glucose monitoring in adults and adolescents with type 1 diabetes?**

OPTION **DIFFERENT FREQUENCIES OF BLOOD GLUCOSE SELF-MONITORING**

Glycaemic control

Compared with intermittent monitoring Continuous blood glucose monitoring (allowing real-time insulin adjustments) may be more effective than home monitoring with a blood glucose meter at improving glycaemic control at 26 weeks in adults aged 25 years or older who were able to wear and replace a sensor effectively, but we don't know about in people aged 15 to 24 years (low-quality evidence).

Note

We found no direct evidence from RCTs on the effects of different frequencies of self blood glucose monitoring versus each other.

For GRADE evaluation of interventions for diabetes: glycaemic control in type 1, see table, p 22 .

Benefits:

Different frequencies of self blood glucose monitoring versus each other:

We found no systematic review or RCTs specifically evaluating the effects of different frequencies of blood glucose self-monitoring in adults or adolescents.

Continuous blood glucose monitoring versus intermittent/conventional monitoring: Adults and adolescents

We found no systematic review but found two RCTs published in three reports. [41] [42] [43]

The first RCT (322 adults and children, type 1 diabetes for at least 1 year, receiving intensive insulin therapy, glycated haemoglobin level 7–10%) compared continuous glucose monitoring system (CGM) versus home monitoring with a capillary blood glucose meter. [41] Participants were stratified a priori into three age groups: 25 years or more, 15 to 24 years, and 8 to 14 years. We have only reported the results for the 15 to 24 years and 25 years and older age groups here. Eligibility for the study was dependent on the participant's ability to wear and replace a sensor effectively (see comment below). Both groups were provided with written instructions on how to use the data to make real-time adjustments of insulin doses and on the use of computer software (for those with a home computer) to retrospectively review the glucose data to alter future insulin doses. Both groups had the same target pre-meal glucose values [3.9 mmol/L to 7.2 mmol/L), peak postprandial values (<10.0 mmol/L), and bedtime or overnight values (5.6 mmol/L to 8.3 mmol/L). The RCT found that in adults 25 years and older, CGM significantly reduced mean glycated haemoglobin level compared with home monitoring at 26 weeks (98 people, mean age 41–44 years, about 84% on insulin pump: mean difference in change –0.53%; 95% CI –0.71% to –0.35%; P <0.001). It found that CGM significantly increased the proportion of people who achieved the target glycated haemoglobin level of <7.0% and significantly increased the time within the target glucose range of 3.9 mmol/L to 10 mmol/L at 26 weeks (<7.0% glycated haemoglobin: 17/52 [33%] with CGM *v* 4/46 [9%] with control; P = 0.005; target range, mean minutes per day, baseline to 26 weeks: 854–986 minutes with CGM *v* 811–840 minutes with control; P <0.001). In the 15- to 24-year age group, the RCT found no significant difference between groups in mean glycated haemoglobin level (110 people, mean age 18.2–18.8 years, 70% on insulin pump: mean difference in change +0.08, 95% CI –0.17 to +0.33; P = 0.52), or in the proportion of participants achieving the target glycated haemoglobin level of <7.0% (P = 0.80) or in increasing the time within the target glucose range of 3.9 mmol/L to 10 mmol/L (P = 0.79). [41] However, use of the CGM sensor was significantly greater in people in the 25 years and older age group compared with the other two age groups (P <0.001; see comment below).

The second RCT (129 adults and children, receiving intensive insulin therapy, about 86% using pump, baseline HbA1c <53 mmol/mol [<7.0%], 67/129 [52%] aged 25 years or older, 33/129 [26%] aged 15–24 years, 29/129 [22%] aged 8–14 years) compared continuous (CGM) versus standard glucose monitoring for 26 weeks. [42] It was performed by the same research group as the first RCT and used a similar methodology, including information on how to use the data to make real-time insulin dose adjustments (see above). Unlike the first RCT, it reported overall results and did

not present data by individual age group. The RCT included a highly selected group with entry HbA1c <53 mmol/mol (<7.0%) and with frequent attention to intensive diabetes management, testing their blood glucose about 7 times a day. The RCT found that CGM significantly reduced HbA1c compared with control at 26 weeks (from 0 to 26 weeks: 47 mmol/mol to 47 mmol/mol [6.4% to 6.4%] with CGM *v* 48 mmol/mol to 51 mmol/mol [6.5% to 6.8%] with control; difference –3.7 mmol/mol, 95% CI –5.3 mmol/mol to –2.2 mmol/mol [–0.34%, 95% CI –0.49% to –0.2%]; P <0.001). [42] It should be noted that both groups had tight control at the start of the trial.

We found a further follow-up report, [43] which reported outcomes at 1 year for people aged 25 years and older who had received CGM and who had been included in both RCTs. [41] [42] However, it did not report further outcomes on people in the control group (see comments below).

Harms:

Different frequencies of self blood glucose monitoring versus each other:
We found no systematic review or RCTs.

Continuous blood glucose monitoring versus intermittent/conventional monitoring: Adults and adolescents
The incidence of adverse events was low in both RCTs, and there were no deaths reported in either RCT. [41] [42] The first RCT found no significant difference in severe hypoglycaemia between groups (severe hypoglycaemic event, events per 100 person-years: age 25 years or older, P = 0.66; age 15–24 years, P = 0.64; severe hypoglycaemic episode with seizure or coma: age 25 years or older, P = 0.85; age 15–24 years, P = 0.14). [41] However, the study was not powered to detect a difference in severe hypoglycaemia. The second RCT reported that 7 people (10%) with CGM and 7 (11%) with control had at least one severe hypoglycaemic event, with no significant difference between groups (further details not reported). [42] The RCT reported that no serious adverse events were attributable to the study interventions. The RCT found no significant difference between groups in median time per day with a glucose level of 3.9 mmol/L or lower at 26 weeks (from 0 to 26 weeks: 91 to 54 minutes per day with CGM *v* 96 to 91 minutes per day with control; P = 0.16). However, the RCT performed several different statistical tests to account for skewness of data, and the result was of borderline significance in one of these. The RCT reported that results in the three prespecified age groups were similar to those in the overall analysis, but did not report any further data. The RCT found lower median time per day between groups favouring CGM for more severe definitions of hypoglycaemia, but differences between groups did not reach significance (from 0 to 26 weeks, 3.3 mmol/L or lower: 40 to 18 minutes per day with CGM *v* 40 to 35 minutes per day with control; P = 0.05; from 0 to 26 weeks, <2.8 mmol/L: 7 to 4 minutes per day with CGM *v* 9 to 8 minutes per day with control; P = 0.12). However, the RCT performed several different statistical tests to account for skewness of data, and the result was significant in some of these. [42]

Comment:

Sensor use:
In the first RCT, there was a significant difference in use of sensor in different age groups in people in the CGM group (results presented graphically, reported as use in 25 years and older group *v* other two age groups; P <0.001). [41] In the CGM group, 83% of people who were 25 years or older used the sensor at least 6 days a week, compared with 30% who were 15 to 24 years of age, and 50% who were 8 to 14 years of age. Perhaps, unsurprisingly, the benefit of CGM was only seen in the group with the highest sensor use. By comparison, the second RCT that recruited a seemingly highly motivated group of people with type 1 diabetes demonstrated high rates of sensor use in all the studied age groups (median CGM use: 6.8 days a week in the 25 years or older group *v* 6.2 days a week in those aged 15–24 years *v* 6.4 days a week in those aged 8–14 years; P = 0.07). [42] It is also worth noting that both of these studies used all the three CGM devices that are currently commercially available in the US.

Follow-up of people who had received CGM:
The follow-up study of 83/86 (97%) people aged 25 years or older who had received CGM from both the RCTs found a significant reduction in mean HbA1c level in people who had had baseline HbA1c of 53 mmol/mol (7.0%) or more at 12 months (49 people, mean change from 0 to 12 months: 60 mmol/mol to 54 mmol/mol [7.6% to 7.2%]; P <0.001). [43] It found no significant difference in people who had had baseline HbA1c 53 mmol/mol (7.0%) or less (34 people, mean change from 0 to 12 months: 47 mmol/mol to 47 mmol/mol [6.4% to 6.4%]; P value not reported). At 12 months, median CGM use was 6.8 days a week. [43]

Clinical guide:
The first commercially available subcutaneous CGM systems were introduced in 1999. These devices measure the glucose level of the interstitial fluid and are based on the premise that interstitial glucose levels correlate closely with blood glucose because of diffusion across the capillary wall. Typically, there is a lag of between 7–15 minutes for the interstitial glucose level to equilibrate with the capillary levels. The first generation of devices were of the "Holter" type, which recorded the

interstitial glucose values but needed computer software to analyse and present the glucose data. These systems were limited to retrospective review of glucose levels. The current generation of CGM devices are "real-time", with a display of the glucose values available continuously to the user. These devices are also equipped with various alarm systems to alert the user of rising or falling glucose levels. In addition, using the software provided with these devices, it is possible to obtain graphical view of blood glucose over extended periods. This is particularly useful in recognising broad patterns of glucose excursions including overnight variations of blood glucose. The sensors used in these devices contain glucose oxidase or similar enzymes. In the presence of these enzymes, glucose is converted to gluconic acid and hydrogen peroxide. The resulting change in electrical charge produced is directly proportional to the concentration of glucose. The accuracy of the devices has improved but CGM devices are still not intended to be used on their own, without adjunctive standard finger-prick blood glucose testing. In addition, these systems need calibration at prespecified intervals using standard finger-prick blood glucose testing. Currently available sensors have a life span of 3 to 7 days, after which they need to be replaced.

The studies reported above show that if used appropriately, CGM can be effective at both improving glycaemic control as well as at reducing hypoglycaemia. However, users of these devices need to be motivated and prepared to wear the sensor most of the time. They should be able to insert and replace the sensors and, perhaps most importantly, effectively use the data made available by the sensors (including use of computer software) to make treatment decisions. It is likely that technological advancements over the next decade will further improve CGM systems and these devices will become more widely used.

OPTION CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII) VERSUS MULTIPLE DAILY SUBCUTANEOUS INSULIN INJECTIONS (MDI)

Glycaemic control

Continuous subcutaneous insulin infusion compared with multiple daily subcutaneous insulin injections Continuous subcutaneous insulin infusion may be more effective than multiple daily subcutaneous insulin injections at improving glycaemic control in adults with type 1 diabetes, but we don't know about in adolescents (very low-quality evidence).

Quality of life

Continuous subcutaneous insulin infusion compared with multiple daily subcutaneous insulin injections Continuous subcutaneous insulin infusion may be more effective than multiple daily subcutaneous insulin injections at improving some quality of life measures in adults with type 1 diabetes. However, evidence was weak, and we don't know about in adolescents (very low-quality evidence).

Note

Some studies found an increase of diabetic ketoacidosis associated with the use of insulin pumps; however, this was in older studies and was not reported in more contemporary studies using modern pumps. People using continuous subcutaneous insulin infusion remain at increased risk of ketosis if the insulin delivery is interrupted for any reason. We found no evidence regarding the effects of continuous subcutaneous insulin infusion on long-term complications/outcomes. A limitation of the current evidence is the limited number of studies that examined current insulin regimens.

For GRADE evaluation of interventions for diabetes: glycaemic control in type 1, see table, p 22 .

Benefits:

Continuous subcutaneous insulin infusion versus multiple daily subcutaneous insulin injections:

Adults

We found 5 systematic reviews (search dates 2005, [44] 2006, [45] 2007, [46] [47] and 2009, [48]) and one subsequent RCT [49] comparing continuous subcutaneous insulin infusion (CSII) versus multiple daily subcutaneous injections (MDI). The reviews performed slightly different analyses, had different inclusion criteria, and reported on different outcomes. Most RCTs were open label, and most were old and did not use contemporary regimens (pumps, insulins).

The first review (search date 2007) included 17 RCTs (908 adults) comparing CSII (applied 24 hours/day; pump therapy during night only excluded) versus MDI using the same short-acting insulin in both treatment groups and reporting on glycated haemoglobin (HbA1 or HbA1c). [46] Seven RCTs were of parallel design and 10 RCTs were a crossover design, and study duration ranged from 5 weeks to 24 months. Insulin therapy was classified as MDI only if at least 50% of participants in the comparator group had three or more injections of short-acting insulin per day. In total, 12 RCTs used regular human or porcine insulin and 5 RCTs used insulin analogues as the short-acting insulin for CSII and MDI. Two studies used an insulin analogue (glargine) as the background insulin. Most studies were of low methodological quality (graded C, defined as "plausible bias seriously weakening confidence in the results"). Because of methodological deficiencies, only 12 RCTs were included in the meta-analysis (6 measured HbA1c and 6 measured HbA1). The review

found that CSII significantly improved glycated haemoglobin compared with MDI (12 RCTs; SMD –0.6, 95% CI –0.87 to –0.22; corresponding to an effect size of –0.6% in original units; absolute numbers not reported; results presented graphically). There was significant heterogeneity among RCTs in the analysis (reported as P = 0.000). The review reported that this was probably caused by several factors (studies dating back to 1982, weak methods, different study designs, different CSII pumps). [46]

The second review (search date 2007) included 21 RCTs. [47] It included RCTs in adults (18 years or older with diabetes for at least 1 year) with a minimum of 12 weeks' treatment duration. In total, 8 RCTs were of crossover design and 13 RCTs were of parallel design. By contrast with the first review, this review compared CSII versus both multiple injections and conventional insulin treatment (CIT). Although not clearly defined in the review, the conventional therapy group is likely to contain people taking less than three injections per day, while the MDI group was on three or more injections per day. Overall, the review found that CSII significantly reduced HbA1c compared with the MDI and CIT groups combined (21 RCTs; 13.2 mmol/mol, 95% CI 8.0 mmol/mol to 17.5 mmol/mol [1.2%, 95% CI 0.73% to 1.59%]; P <0.001; results presented graphically). [47] In a subgroup analysis, CSII significantly reduced HbA1c compared with either group alone (CSII *v* CIT: 15.4 mmol/mol, 95% CI 9.4 mmol/mol to 22.0 mmol/mol [1.4%, 95% CI 0.95% to 2.00%]; P <0.001; CSII *v* MDI: 7.7 mmol/mol, 95% CI 0.9 mmol/mol to 14.3 mmol/mol [0.7%, 95% CI 0.08% to 1.30%]; P = 0.03; absolute numbers not reported). [47]

The third review (search date 2009) included 23 RCTs (976 people). [48] Only studies using three or more injections in the MDI arm were eligible. In total, 11 RCTs were of parallel design and 12 RCTs had a crossover design. Of these, 14 RCTs (61%) were industry sponsored. Eleven RCTs used an insulin analogue as the rapid-acting insulin in the MDI arm while 4 RCTs used glargine as the long-acting insulin. Data from 6 crossover studies were re-analysed by the review. Out of 23 RCTs, 7 RCTs included people under the age of 18 years, including children. We have only reported data for those aged 18 years or older here. The review found that CSII significantly reduced HbA1c compared with MDI (12 RCTs; mean difference –3.2 mmol/mol, 95% CI –5.7 mmol/mol to –0.07 mmol/mol [–0.29%, 95% CI –0.52% to –0.06%]; P = 0.013; results presented graphically; absolute numbers not reported). There was significant heterogeneity among RCTs in the analysis (P = 0.002). The review did not explain the heterogeneity, but noted that in the overall analysis of all age groups for HbA1c, the removal of one RCT in adults with a high risk of bias reduced heterogeneity considerably. Quality of life was measured using different instruments by 15 RCTs (including Diabetes Treatment Satisfaction Questionnaire [DTSQ], Diabetes Quality of Life [DQOL], and Diabetes Quality of Life for Youth [DQOLY]). The review did not pool data. Results varied by the questionnaire used, and the review noted that it was difficult to determine which treatment was better when independent questionnaires were used to measure satisfaction, acceptability, preferred treatment, and reaction to treatment. However, the review reported that the majority of participants were more satisfied with CSII than with MDI.

The subsequent RCT also assessed the difference in glycaemic control when people using NPH insulin-based MDIs were randomised either to an MDI regimen with insulin glargine as basal insulin and meal-time insulin lispro or to continuous subcutaneous infusion of insulin lispro and managed on either regimen for 6 months. [49] Fifty people were randomised, and 43 (86%) people completed the study. The RCT found no significant difference between groups in mean HbA1c (baseline-adjusted difference –1.1 mmol/mol, 95% CI –5.5 mmol/mol to +3.3 mmol/mol [−0.1%, 95% CI −0.5% to +0.3%]). Similarly, fasting blood glucose and other pre-prandial, post-prandial, and night-time self-monitored plasma glucose levels did not differ between the regimens, nor did measures of plasma glucose variability. [49]

The fourth review (search date 2005) included both RCT and observational data and reported on quality of life outcomes. [44] The review did not pool data because of weak methods and inconsistent analysis among included studies. It found 5 RCTs, of which two were in adults. One RCT (27 people) found no significant difference between groups in quality of life measures at 9 months (DQOL questionnaire, reported as no significant difference on any of the subscales; P values not reported). One RCT (79 adults) with a high withdrawal rate (22%) found that scores on the short form-36 subscales of general health and mental health improved significantly in the CSII group compared with the MDI group (general health: +5.9 with CSII *v* –1.2 with MDI; P = 0.048; mental health: +5.2 with CSII *v* –0.6 with MDI; P = 0.05; further details not reported). The review reported one further RCT (272 people) published after its search date, which found significantly higher quality of life score for CSII compared with MDI at the end of treatment (overall DQOL score: 75 with CSII *v* 71 with MDI; P less-than or equal to0.001). The review noted that the MDI group did not use a long-acting insulin analogue, and did not take into account any disappointment effect for participants who did not receive their preferred treatment and had thus withdrawn. [44]

The fifth review (search date 1996–2006) only included RCTs of >6 months' duration of CSII and where the rate of severe hypoglycaemia during MDI was >10 episodes per 100 patient-years of treatment. [45] The review reported that only RCTs published after 1996 were eligible — because the review wished to examine modern pumps and insulins in people with a significant initial rate of hypoglycaemia (the target population in some guidelines) — and which had an adequate duration of pump therapy. All the RCTs included in the review used isophane or lente insulins in the MDI arm. Severe hypoglycaemia was defined as that requiring third-party assistance including unconsciousness, seizure, glucagon administration, and emergency attendance or admission to hospital. The review included 22 studies in total, including 10 studies in children or adolescents and 12 in adults. The review included both parallel-design RCTs and crossover studies in which people were switched from MDI to CSII and acted as their own control, but we have only reported the outcome data for RCTs here. The review found 6 RCTs (431 people in total; 380 [88%] adults and 51 [12%] children). The review found that insulin pump therapy significantly reduced HbA1c compared with control (difference 2.1 mmol/mol, 95% CI 1.3 mmol/mol to 3.3 mmol/mol [0.21%, 95% CI 0.13% to 0.30%]; absolute numbers not reported; RCTs in analysis not reported). [45] However, these data may have also included children. The review also pooled data on hypoglycaemia (see harms).

Adolescents

We found no systematic review or RCTs in adolescents alone.

Harms:

Continuous subcutaneous insulin infusion versus multiple daily subcutaneous insulin injections:

Adults

We also found some data on the occurrence of ketoacidosis with the use of earlier insulin pumps (see harms of intensive treatment programmes, p 3).

The first review did not pool data for hypoglycaemic episodes because of small numbers and differences between RCTs. [46] It reported that severe hypoglycaemic episodes were rare. Three RCTs reported that no severe hypoglycaemia was observed. Of the RCTs that reported episodes, the proportion of people with severe hypoglycaemia ranged from 0 to 0.13 in the CSII groups and from 0 to 0.4 in the MDI group (further details not reported). Of 6 RCTS that reported episodes, the rate of people with mild/minor hypoglycaemic events ranged from 0.9 to 3.1 weekly events per person in the CSII groups and from 1.1 to 3.3 weekly events per person in the MDI group (median rate: 1.9 weekly events per person with CSII *v* 1.7 weekly events per person with MDI; statistical analysis not reported). The review reported that overall, information on adverse effects other than hypoglycaemia was insufficient in the available publications. Data on ketoacidosis were reported in 10 RCTs. Only one RCT reported a statistically significant increase in ketoacidosis with MDI compared with both CSII groups (fixed and variable infusion rate), but this RCT was excluded from the analysis because of major methodological deficiencies. [46] Other adverse effects reported included infusion site problems with CSII.

The second review reported that overall there was no significant difference in the frequency of hypoglycaemic events between CSII and MDI/CIT groups, although no analysis or further data were reported to support this finding. [47]

The third review reported that included RCTs used different scales for non-severe and severe hypoglycaemic events, which precluded the pooling of data. [48] It reported that generally (including all RCTs both in people older than and younger than 18 years), data indicated that there was no relevant benefit of one intervention over the other for reducing non-severe hypoglycaemia, but that CSII may be better than MDI for reducing the incidence of severe hypoglycaemic events. However, this conclusion was based on a general overview of events reported in individual RCTs. The review noted that adverse events in general were not well reported. It found reports of injection site and infusion site injuries, infusion site infections, blockages, and dislodgements, but did not report a statistical analysis between groups. It reported that in two RCTs, there was one episode of ketoacidosis in the CSII group of each study, and one episode in the MDI group in one of the RCTs. [48]

In the subsequent RCT, participants on CSII recorded 1152 hypoglycaemic events (by 23/28 [82%] people) compared with 1022 hypoglycaemic events (by 27/29 [93%] people) recorded in the MDI group. [49] The RCT found no significant difference in hypoglycaemia-related outcomes between groups (overall, P = 0.93; non-severe, P = 0.97; nocturnal, P = 0.34; symptomatic, P = 0.84; asymptomatic, P = 0.95). [49]

The fourth review did not report on adverse effects. [44]

The fifth review, which included more recent studies (search date 1996–2006) pooled data for hypoglycaemic events. [45] The review found that CSII significantly reduced severe hypoglycaemia compared with MDI (RR 2.89, 95% CI 1.45 to 5.76; absolute numbers not reported). However,

these data may include children. The review did not perform a separate analysis based on age, but mean age was a significant predictor of treatment effect (P = 0.019), with older participants having a greater reduction in severe hypoglycaemia on CSII compared with MDI (results presented graphically). [45]

Adolescents
We found no RCTs.

Comment:

Clinical guide:
Continuous subcutaneous insulin infusion (CSII) has been available for >30 years and has been a valuable tool in the management of type 1 diabetes. Over time, the reliability and functionality of insulin pumps have improved, with some of the newer pumps also having additional features such as insulin bolus calculators, ability to modify the rate of delivery of meal-time insulin bolus (square wave and dual wave bolus), and display of continuous glucose measurements obtained via a separate sensor to facilitate insulin dose adjustments and hypoglycaemia monitoring. Furthermore, clinical resources including trained healthcare professionals and structured education programmes are increasingly available to the individual insulin pump user.

The evidence presented here based on available RCT data shows that use of CSII in broad adult populations with type 1 diabetes is associated with a relatively modest, albeit clinically significant, improvement in glycaemic control as measured by HbA1c in the range of 3.3 mmol/mol to 7.7 mmol/mol (0.3% to 0.7%). CSII may offer improvement in health-related quality of life outcomes and may reduce the frequency of severe hypoglycaemia in those at highest risk. The available evidence does not support a reduction in non-severe hypoglycaemia.

Although we have not reported on observational studies, overall, these studies have shown a much greater benefit with CSII than that observed in RCTs. Results of the observational studies were included by NICE in the development of the recent insulin pump therapy guidance. [50] The inclusion of non-randomised studies was based on the premise that people enrolled in observational studies would more closely resemble CSII users in routine clinical practice. The guidance also mentioned that specific but infrequent complications of CSII included reactions and occasional infection of the cannula site, tube blockage, and pump malfunction.

One of the limitations of the available systematic reviews is the limited number of RCTs that used long-acting insulin analogues in the MDI arm. The available evidence from the few such studies shows no difference between CSII and MDI in terms of HbA1c. Furthermore, there is insufficient evidence regarding the effects of long-term CSII use on complications and mortality.

Reassuringly, the reported increased risk of diabetic ketoacidosis with the earlier generations of pump devices does not seem to be apparent in more recent studies. This may reflect both improvements in technology and improved delivery of patient education. People using CSII remain at increased risk of ketosis if the insulin delivery is interrupted for any reason.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Psychological interventions New option. [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [38] [37] [39] [40] We found insufficient evidence on the effects of psychological interventions on glycaemic control. We found some evidence that psychological interventions may be more effective than control at improving some psychological outcome measures. However, evidence was weak, inconsistent, varied by the specific intervention used, and by the outcome measure assessed. Categorised as Unknown effectiveness.

Educational interventions New evidence added. [22] Categorisation unchanged (Likely to be beneficial).

Intensive treatment programmes New evidence added. [7] [8] [9] [13] [14] [15] [16] Categorisation unchanged (Likely to be beneficial).

Continuous subcutaneous insulin infusion (CSII) versus multiple daily subcutaneous insulin injections (MDI) New evidence added. [44] [45] [46] [47] [48] [49] [50] Categorisation changed from Trade-off between benefits and harms to Likely to be beneficial.

Different frequencies of blood glucose self-monitoring New comparison added (continuous blood glucose monitoring versus intermittent/conventional monitoring). [41] [42] [43] Categorisation changed from Unknown effectiveness to Likely to be beneficial.

REFERENCES

1. Verge CF, Gianini R, Kawasaki E, et al. Predicting type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. *Diabetes* 1996;45:926–933.[PubMed]
2. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Geneva: World Health Organization, 1999.
3. International Diabetes Federation. The diabetes atlas, 4th ed. Brussels: International Diabetes Federation, 2009.
4. Patterson CC, Dahlquist GG, Gyurus E, et al. Incidence trends for childhood type 1 diabetes in Europe during 1989–2003 and predicted new cases 2005–20: a multicentre prospective registration study. *Lancet* 2009;373:2027–2033.[PubMed]
5. DIAMOND Project Group. Incidence and trends of childhood type 1 diabetes worldwide 1990–1999. *Diabet Med* 2006;23:857–866.[PubMed]
6. Betterle C, Zanette F, Pedini B, et al. Clinical and subclinical organ-specific autoimmune manifestations in type 1 (insulin-dependent) diabetic patients and their first-degree relatives. *Diabetologia* 1984;26:431–436. [PubMed]
7. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986.[PubMed]
8. Wang PH, Lau J, Chalmers TC, et al. Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. *Lancet* 1993;341:1306–1309.[PubMed]
9. Stettler C, Allemann S, Juni P, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. *Am Heart J* 2006;152:27–38.[PubMed]
10. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *New Engl J Med* 2005;353:2643–2653.[PubMed]
11. Martin CL, Albers J, Herman WH, et al. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care* 2006;29:340–344.[PubMed]
12. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 2003;290:2159–2167.[PubMed]
13. Pop-Busui R, Low PA, Waberski BH, et al. Effects of prior intensive insulin therapy on cardiac autonomic nervous system function in type 1 diabetes mellitus: The diabetes control and complications trial/epidemiology of diabetes interventions and complications study (DCCT/EDIC). *Circulation* 2009;119:2886–2893.[PubMed]
14. de Boer I, Kestenbaum B, Rue TC, et al. Insulin therapy, hyperglycemia, and hypertension in type 1 diabetes mellitus. *Arch Intern Med* 2008;168:1867–1873.[PubMed]
15. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr* 1994;125:177–188.[PubMed]
16. White NH, Cleary PA, Dahms W, et al. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J Pediatr* 2001;139:804–812.[PubMed]
17. The Diabetes Control and Complications Trial Research Group. Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the Diabetes Control and Complications Trial. *Diabetes Care* 2001;24:1711–1721.[PubMed]
18. Egger M, Davey Smith G, Stettler C, et al. Risks of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med* 1997;14:919–928.[PubMed]
19. Loveman E, Cave C, Green C, et al. The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation. *Health Technol Assess* 2003;7: iii, 1–190.[PubMed]
20. Terent A, Hagfall O, Cederholm U. The effect of education and self-monitoring of blood glucose on glycosylated hemoglobin in type I diabetes. A controlled 18-month trial in a representative population. *Acta Med Scand* 1985;217:47–53.[PubMed]
21. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ* 2002;325:746–749.[PubMed]
22. George JT, Valdovinos AP, Russell I, et al. Clinical effectiveness of a brief educational intervention in type 1 diabetes: Results from the BITES (Brief Intervention in Type 1 diabetes, Education for Self-efficacy) trial. *Diabet Med* 2008;25:1447–1453.[PubMed]
23. Hampson SE, Skinner TC, Hart J, et al. Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review. *Health Technol Assess* 2001;5:1–79.[PubMed]
24. Bott S, Bott U, Berger M, et al. Intensified insulin therapy and the risk of severe hypoglycaemia. *Diabetologia* 1997;40:926–932.[PubMed]
25. National Institute for Health and Clinical Excellence. Diabetes (types 1 and 2) - patient education models: Guidance. 2003; TA60. Available at: http://www.nice.org.uk/TA60 (last accessed 19 April 2011).
26. National Institute for Health and Clinical Excellence. CG15 Type 1 diabetes in adults: Full guideline, main section. 2004. Available at: http://www.nice.org.uk/CG15 (last accessed 19 April 2011).
27. Winkley K, Ismail K, Landau S, et al. Psychological interventions to improve glycaemic control in patients with type 1 diabetes: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2006;333:65.[PubMed]
28. Amsberg S, Anderbro T, Wredling R, et al. A cognitive behavior therapy-based intervention among poorly controlled adult type 1 diabetes patients – a randomized controlled trial. *Patient Educ Couns* 2009;77:72–80.[PubMed]
29. Ismail K, Thomas SM, Maissi E, et al. Motivational enhancement therapy with and without cognitive behavior therapy to treat type 1 diabetes: a randomized trial. *Ann Intern Med* 2008;149:708–719.[PubMed]
30. Snoek FJ, van der Van NC, Twisk JW, et al. Cognitive behavioural therapy (CBT) compared with blood glucose awareness training (BGAT) in poorly controlled Type 1 diabetic patients: long-term effects on HbA1c moderated by depression. A randomized controlled trial. *Diabet Med* 2008;25:1337–1342.[PubMed]
31. Schachinger H, Hegar K, Hermanns N, et al. Randomized controlled clinical trial of Blood Glucose Awareness Training (BGAT III) in Switzerland and Germany. *J Behav Med* 2005;28:587–594.[PubMed]
32. van der Ven NC, Hogenelst MH, Tromp-Wever AM, et al. Short-term effects of cognitive behavioural group training (CBGT) in adult Type 1 diabetes patients in prolonged poor glycaemic control. A randomized controlled trial. *Diabet Med* 2005;22:1619–1623.[PubMed]
33. Fosbury JA, Bosley CM, Ryle A, et al. A trial of cognitive analytic therapy in poorly controlled type I patients. *Diabetes Care* 1997;20:959–964.[PubMed]
34. Nansel TR, Iannotti RJ, Simons-Morton BG, et al. Long-term maintenance of treatment outcomes: diabetes personal trainer intervention for youth with type 1 diabetes. *Diabetes Care* 2009;32:807–809.[PubMed]
35. Wysocki T, Harris MA, Buckloh LM, et al. Randomized, controlled trial of Behavioral Family Systems Therapy for Diabetes: maintenance and generalization of effects on parent-adolescent communication. *Behav Ther* 2008;39:33–46.[PubMed]
36. de Wit M, Delemarre-van de Waal HA, Bokma JA, et al. Monitoring and discussing health-related quality of life in adolescents with type 1 diabetes improve psychosocial well-being: a randomized controlled trial. *Diabetes Care* 2008;31:1521–1526.[PubMed]
37. Ellis DA, Yopp J, Templin T, et al. Family mediators and moderators of treatment outcomes among youths with poorly controlled type 1 diabetes: results from a randomized controlled trial. *J Pediatr Psychol* 2007;32:194–205.[PubMed]
38. Ellis D, Naar-King S, Templin T, et al. Multisystemic therapy for adolescents with poorly controlled type 1 diabetes: reduced diabetic ketoacidosis admissions and related costs over 24 months. *Diabetes Care* 2008;31:1746–1747.[PubMed]
39. Ellis DA, Naar-King S, Frey M, et al. Multisystemic treatment of poorly controlled type 1 diabetes: effects on medical resource utilization. *J Pediatr Psychol* 2005;30:656–666.[PubMed]
40. Channon SJ, Huws-Thomas MV, Rollnick S, et al. A multicenter randomized controlled trial of motivational interviewing in teenagers with diabetes. *Diabetes Care* 2007;30:1390–1395.[PubMed]
41. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Group, Tamborlane WV, Beck RW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464–1476.[PubMed]
42. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Group, Beck RW, Hirsch IB, et al. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care* 2009;32:1378–1383.[PubMed]
43. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Bode B, Beck RW, et al. Sustained benefit of continuous glucose monitoring on A1C, glucose profiles, and hypoglycemia in adults with type 1 diabetes. *Diabetes Care* 2009;32:2047–2049.[PubMed]
44. Barnard KD, Lloyd CE, Skinner TC, et al. Systematic literature review: quality of life associated with insulin pump use in type 1 diabetes. *Diabet Med* 2007;24:607–617.[PubMed]
45. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med* 2008;25:765–774.[PubMed]
46. Jeitler K, Horvath K, Berghold A, et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia* 2008;51:941–951.[PubMed]
47. Jacobsen IB, Henriksen JE, Hother-Nielsen O, et al. Evidence-based insulin treatment in type 1 diabetes mellitus. *Diabetes Res Clin Pract* 2009;86:1–10.[PubMed]
48. Misso ML, Egberts KJ, Page M, et al. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. In: The Cochrane Library, Issue 1, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2009.
49. Bolli GB, Kerr D, Thomas R, et al. Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in type 1 diabetes: a randomized open parallel multicenter study. *Diabetes Care* 2009;32:1170–1176.[PubMed]
50. National Institute for Health and Clinical Excellence. Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus. July 2008. Technical appraisal 151. Available at: http://www.nice.org.uk/TA151 (last accessed 19 April 2011).

Diabetes: glycaemic control in type 1

Lalantha Leelarathna
Clinical Research Associate and Honorary Clinical Fellow
Institute of Metabolic Science
University of Cambridge and Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital
Cambridge
UK

Rustom Guzder
Consultant Endocrinologist
Nanaimo Regional General Hospital
Nanaimo, BC
Canada

Koteshwara Muralidhara
Consultant Diabetologist
Birmingham Community Healthcare NHS Trust
Birmingham
UK

Mark Lewis Evans
University Lecturer and Honorary Consultant Physician
Institute of Metabolic Science
University of Cambridge and Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital
Cambridge
UK

Competing interests: MLE has been reimbursed for attending symposia and scientific meetings from Roche, Eli Lilly, and Medtronic. He has received fees for speaking and writing reviews for Medtronic, and consultancy fees from Medtronic and Cellnovo. He has had support for trials of medical devices from Roche and Medtronic, and has stock-holding options with Cellnovo. LL, RG, and KM declare that they have no competing interests.
We would like to acknowledge the previous contributors of this review: Bala Srinivasan, Ian Lawrence, and Melanie Davies.

Disclaimer

TABLE **GRADE evaluation of interventions for diabetes: glycaemic control in type 1**

Important outcomes	Mortality, long-term outcomes (microvascular), long-term outcomes (macrovascular), glycaemic control, quality of life, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of intensive treatment programmes, psychological interventions, and educational interventions in adults and adolescents with type 1 diabetes?									
At least 14 (at least 2067) [9] [18]	Mortality	Intensive *v* conventional treatment programme	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for restricted population (young people at low risk of macrovascular events) in 1 review
At least 8 (at least 1712) [8] [15] [7]	Long-term outcomes (microvascular)	Intensive *v* conventional treatment programme	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
7 (unclear) [9]	Long-term outcomes (macrovascular)	Intensive *v* conventional treatment programme	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for use of composite outcome (including fatal and non-fatal events)
At least 2 (at least 1441) [8] [9] [15] [7]	Glycaemic control	Intensive *v* conventional treatment programme	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
At least 15 (at least 2469) [8] [18] [15] [7]	Adverse effects	Intensive *v* conventional treatment programme	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inconsistent results depending on when RCT undertaken (older version of insulin pumps compared with more contemporary pumps) affecting generalisability of results
15 (896) [22] [23] [20] [21]	Glycaemic control	Educational interventions *v* usual care/controls	4	−1	−1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
10 (at least 286) [22] [21] [23]	Quality of life	Educational interventions *v* usual care/controls	4	−1	0	−2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for heterogeneity of interventions and lack of standardised or validated outcome measures
20 (1584) [27] [28] [29] [30] [31] [32] [33] [34] [36] [37] [40]	Glycaemic control	Psychological interventions *v* control	4	−2	−1	0	0	Very low	Quality points deducted for incomplete reporting of results and weak methods. Consistency point deducted for significant heterogeneity
14 (at least 953) [27] [28] [29] [30] [32] [33] [35] [36] [37] [40]	Quality of life	Psychological interventions *v* control	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and weak methods. Directness point deducted for results varying by range of outcome measures used/wide range of outcome measures used
What are the effects of different insulin regimens or frequency of blood glucose monitoring in adults and adolescents with type 1 diabetes?									
2 (337) [41] [42]	Glycaemic control	Continuous blood glucose monitoring *v* intermittent/conventional monitoring	4	0	0	−2	0	Low	Directness points deducted for inclusion of children in 1 RCT and highly selected populations (very motivated in 1 RCT; ability to wear and replace sensor effectively in both RCTs)

Important outcomes	Mortality, long-term outcomes (microvascular), long-term outcomes (macrovascular), glycaemic control, quality of life, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
At least 21 (at least 951) [45] [46] [47] [48] [49]	Glycaemic control	Continuous subcutaneous insulin infusion *v* multiple daily subcutaneous insulin injections	4	−2	0	−2	0	Very low	Quality points deducted for incomplete reporting of results and weak methods. Directness points deducted for heterogeneity and some studies using old regimens (pumps, insulins) affecting generalisability of results
At least 15 (at least 378) [44] [48]	Quality of life	Continuous subcutaneous insulin infusion *v* multiple daily subcutaneous insulin injections	4	−2	0	−1	0	Very low	Quality points deducted for incomplete reporting of results and weak methods. Directness point deducted for range of assessment methods used

Type of evidence: 4 = RCT.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.